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The role of polyphenols on bone metabolism in osteoporosis

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ABSTRACT

Osteoporosis is a skeletal disease of bone mass loss and deterioration of the bone structure leading to increased susceptibility to fracture, generally associated with risk factors that include hormonal imbalance, increased oxidative stress and chronic inflammation.
Nutritional factors and certain lifestyle reduce the risks of occurrence of osteoporosis and are part of a number of national and international prevention recommendations. Recent reports based on molecular mechanisms of dietary polyphenols have highlighted the benefits in their prevention and treatment of osteoporosis. Polyphenols can protect bone health through reduction of oxidative stress because they act as antioxidants, reduction of inflammation by proinflammatory signaling, modulation of osteoblastogenesis, osteoclastogenesis, and osteoimmunological action.
This review reports about some important bioactive polyphenol sources and describes their action against osteoporosis based on in vitro and in vivo studies.

1. Introduction

Osteoporosis is a disorder which is characterized by the loss of bone strength and therefore increased risk of fragility fractures, most frequently in the hip, wrist and spine. Osteoporosis is estimated to affect 200 million people worldwide (Kanis, 2007), which equally affects men and women. World Health Organization defines the diagnostic criterion for osteoporosis as a bone mineral density (BMD) of 2.5 SDs below the mean peak bone mass (average of young, healthy adults). The Japanese Society for Bone and Mineral Research slightly revised this criterion for osteoporosis as bone density below 70% of the mean of young adult for women of 20–44 years old, which is approximately equivalent to mentioned T-score (Soen et al., 2013). BMD is associated with ethnic differences, where Asians at every age has the lowest BMD, and Blacks have the highest BMD values (Barrett-Connor et al., 2005). These ethnic differences in absolute fracture risk are important because of set ethnic-specific clinical recommendations. Current diagnosis of osteoporosis is linked to the additional characterization of bone metabolism by the determination of biochemical markers of bone turnover.

Postmenopausal women belong to primary type 1, both women and men after the age of 75 as type 2 and secondary which occurs equally at any age in both men and women. The last type is a result of chronic diseases or medical problems. Trend in age-dependent variation in bone density of women are presented in Fig. 1. The same trends also are followed by men (Soen et al., 2013; Barrett-Connor et al., 2005).

The causes of the incidence of osteoporosis are associated with risk factors, including hormonal imbalance, increased oxidative stress and chronic inflammation (van'T Hof & Ralston, 2001). Numerous studies have examined the mechanisms of the regulation of bone remodeling in addition to the interaction of target hormones, cytokines, growth factors and transcription factors. Calcium metabolism together with estrogens and androgens plays a significant role in bone turnover. Low level of estrogen, e.g. in menopausal women, and low level of testosterone in hypogonadal men increases bone resorption (Cauley, 2015; Funaro, Bolyakov, Gimenez, Herman, & Paduch, 2013).

The prevention of the prevalence of osteoporosis is also linked to lifestyle changes where diet, especially rich in fruit and vegetables, is

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; BMP-4, bone morphogenetic protein 4; c-Fos, transcriptional factor for osteoclastogenesis; cGMP, cyclic GMP; COX, cyclooxygenase; COX-2, cyclooxygenase 2; DYD, deoxypyridinoline; eNOS, endothelial NO synthase; EGCG, (−)-Epigallocatechin-3-gallate; ET-1, endothelin-1; GT, green tea; HO-1, heme-oxygenase-1; IGF-1, insulin-like growth factor-I; IL-6, interleukin 6; IL-1, interleukin 1; iNOS, inducible NO synthase; JNK, c-jun-N-terminal kinase; MAPK, mitogen-activated protein kinase; MC3T3-E1, sub-line of osteoblast precursor cell line derived from *Mus musculus* calvaria; MSC, mesenchymal stem cell; Nfatc1, nuclear factor T cell activator 1; NF-κB, nuclear factor of B cells; OC, osteocalcin; OPG, osteoprotegerin; ORX, orchidectomized; OS, oxidative stress; OVX, ovariectomized; p38, p38 mitogen-activated protein kinase; PINP, procollagen I N-terminal propeptide; RANK/RANKL, receptor activator for nuclear factor κB ligand; ROS, reactive oxygen species; Runx2, Runt-related transcription factor 2; SaOs-2, sarcoma osteogenic cells; SAPK/JNK, specific stress-activated protein kinase pathway; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TRAP, tartrate-resistant acid phosphatase.

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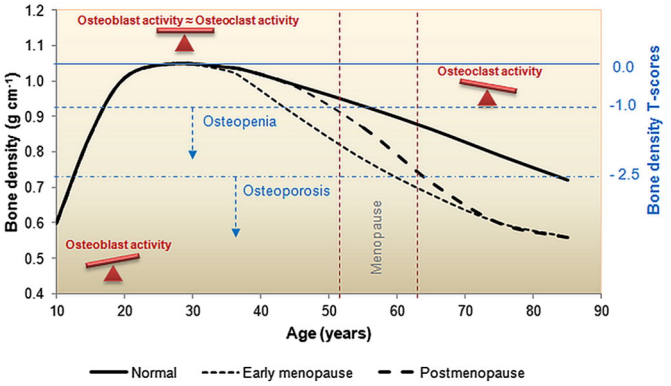

Fig. 1. Age-dependent differences in the bone density of women with normal and risk groups as a result of hormonal disbalance. The World Health Organization has defined osteopenia as a bone density T-score of between −1.0 and −2.5, and osteoporosis as a T-score lower than −2.5.

associated with less bone resorption, and a poor dietary pattern full of processed foods is associated with lower bone mineral density (Hardcastle, Aucott, Reid, & MacDonald, 2011; McNaughton, Wattanapenpaiboon, Wark, & Nowson, 2011). Recently, many studies have found links between dietary phenolic intakes and bone health (Welch & Hardcastle, 2014). Bioactive phenolic compounds such as flavonoids were recognized as health benefit compounds due to their antioxidant and anti-inflammatory properties. Although soy isoflavonoids are structurally similar to estrogen and bind to estrogen receptors (Kinjo et al., 2004), their effects on osteoporosis are still unclear (Taku, Melby, Nishi, Omori, & Kurzer, 2011). These contribute to conflicting results related to differences in study design, estrogen status of the body, metabolism of isoflavones among individuals, and other dietary factors (Atmaca, Kleerekoper, Bayraktar, & Kucuk, 2008).

The present paper will review the recent evidence regarding the role of phenolic compounds in the prevention of bone loss by the mechanism of their influence on bone density.

2. Basic mechanism of bone formation and remodeling

Bone tissue is characterized by specific biomechanical properties of strength and elasticity. It is metabolically active and changes throughout life, from the development and growth of bones during embryonic and fetal life, through maintenance and adaptation of bone mass in physiological conditions during the healing bone damage. Bone morphogenesis and osteogenesis are processes of formation of bone tissue, and the result is the simultaneous construction (bone formation, bone modeling) and degradation (bone resorption) of bone tissue. Construction and destruction of bone tissue, considering their purpose as a whole, are synergistic and balanced physiological processes because both work toward creating and maintaining optimal morphology, or homeostasis of the skeletal system in accordance with the functional requirements (Clarke, 2008).

Bone formation is marked by intense osteoproduction action of osteoblasts and minimized osteoresorption. Bone remodeling (bone reconstruction) in histological terms is a quieter morphogenetic process whereby the intensity of osteoproduction and osteoresorption are identical. Remodeling of bone mass did not change the already existing mass of bone tissue arrangement (Raisz, 2005).

About 25% of cancellous bone substance may be undergoing remodeling annually, but only 3% of compact bone substance (Kini & Nandeesh, 2012). The purpose of bone remodeling is to optimize the architecture of the skeletal system and adapt to the biomechanical demands. It is therefore a dynamic lifelong process that achieves and maintains homeostasis of the skeletal system by changing biomechanical and metabolic conditions.

It is evident that bone loss occurs in the postmenopausal woman as a result of an increase in the rate of bone remodeling and imbalance between the activity of osteoclasts and osteoblasts by the increase in the rate of initiation of new bone remodeling cycles. Remodeling imbalance results in irreversible bone loss. The changes in bone turnover that accompany the menopause connect with direct actions of estrogen on bone cells (Raisz, 2005). Some studies suggest that bone marrow stromal and mononuclear cells are important target cells for sex hormones in metabolic bone. It was found that the age and menstrual status are the predictors with the highest influence on the bone mineral density in women (see Fig. 1). Fruits and vegetables have pleiotropic effects on the bone metabolism with beneficial influence on the minerals such as magnesium, potassium and zinc (Yamaguchi, 2010).

3. Role of oxidative stress in the emerging of bone disease

In general, oxidative stress (OS) is described as the state of imbalance between pro-oxidants and antioxidants. It is believed that there is a relationship between reactive oxygen species (ROS) and its pathogenesis. OS affects the promotion of an increase in bone resorption, differentiation and function of osteoclasts, so it has a significant influence on the occurrence of osteoporosis (Noor, Kania, & Setiawan, 2014; Gao, Ma, Dong, Yong, & Su, 2014). Mitochondria produce ROS and induce a series of retrograde signaling, alter mitochondrial transmembrane potential, activate calcineurin and Ca^{2+} dependent kinases, and induce cell differentiation of osteoclasts (Srinivasan et al., 2010). The increased levels of lipid peroxides and H_2O_2 affected lower activities of antioxidant enzymes, catalase (Cat), glutathione peroxidase (GPx) and superoxide dismutase (SOD) in postmenopausal women with osteoporosis (Ozgocmen, Kaya, Fadillioglu, Aydogan, & Yilmaz, 2007).

The activation of osteoclasts is regulated by different molecular signals (Lee et al., 2005). ROS can promote osteoclast resorption directly by stimulating signaling of osteoclast differentiation and receptor activator of nuclear factor kappa-B (RANK), or indirectly, by stimulating osteoblast/osteoclast coupling and subsequent osteoclast differentiation by receptor activator of nuclear factor kappa-B ligand (RANKL) (see Fig. 2). Osteoprotegerin (OPG) binds RANKL and reduces its ability to bone resorption. RANKL, RANK and OPG are closely linked to the production of proinflammatory molecules, including tumor necrosis factor alpha (TNF-α) (Jagger, Lean, Davies, & Chambers, 2005), interleukin (IL)-1, IL-6 (Sakuma et al., 2000), nitric oxide (NO) (Jung, Lin, Ramos, Faddis, & Chole, 2003) and inflammatory eicosanoids (e.g. PGE2) (Suda et al., 2004). In comparison with an endothelial isoform of nitric oxide synthase (eNOS), which is widely expressed in bone, the inducible NOS (iNOS) is only expressed in response to inflammatory stimuli, where the proinflammatory cytokines (IL-1 and TNF-α) activate the iNOS pathway in bone cells and induce bone loss. In addition, eNOS isoform may prevent osteoporosis through regulating activity of osteoblasts (Atmaca et al., 2008). The resulting ROS are involved as a mediator of RANKL signaling of osteoclastogenesis and osteoclast lifespan. Antioxidants, such as polyphenols, also allow the regulation of bone turnover by reducing the production of inflammatory mediators (Hubert, Lee, Lee, & Chun, 2014).

A close relation between gaseous messenger molecules such as nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) and osteoporosis was found. Many studies on animals and human trials support the concept of bone loss prevention by NO donors, and therefore have been an alternative to estrogen, estrogen agonists–antagonists, and androgen receptor modulator therapy in the prevention and treatment of osteoporosis. It was confirmed that estradiol stimulates NO production in osteocytes, thus leading to increased cyclic GMP (cGMP) synthesis and activation of cGMP-dependent protein kinases (PKGs) (Joshua, Kalyanaraman, Marathe, & Pilz, 2014). CO is enhanced by inducing the enzyme heme-oxygenase-1 (HO-1) in the presence of 17-β-estradiol (Marcantoni et al., 2012). The increasing expression of HO-1 protein and increasing levels of its activity are essential for mesenchymal stem

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